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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/932,678	08/16/2001	Ronald H. Reeder	14538A005810	5058

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EXAMINER	
YU, MISOOK	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 08/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/932,678	Applicant(s) REEDER ET AL.	
	Examiner Misook Yu	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *6 and 25-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I, claims 1-5, 7-19 in Paper No 7 is acknowledged. On reconsideration, group III, claims 20-24, drawn to method of producing Rrn3 protein using the nucleic acid of group I will be rejoined and examined on merits for this office action. However, the rest of invention groups remain restricted for the reasons of record set forth in Paper No. 6. Applicant's traversal for the restriction requirement set forth in Paper No. 6. is on the grounds that the inventions have not been shown to be independent or distinct, and a serious burden on the examiner has not been met. This is not found persuasive. The inventions of the various groups are distinct for the reasons set forth in Paper No. 6 and as to the question of burden of search, the inventions are classified differently, necessitating different searches in class and subclass of the US Patent. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. As for the single inventive concept, the instant application is not a National Stage application filed under 35 USC 371. The "single inventive concept" does not guide US practice. The restriction is proper for the reasons previously set forth.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-38 are pending and claims 1-5, 7-24 are examined on merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,2, 4, 7-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, ***had possession*** of the claimed invention.

The claims are drawn to isolated nucleic acid which hybridizes under the specified conditions in the claims to SEQ ID NO:1 or to DNA encoding SEQ ID NO:2 and also drawn to expression construct, with a transcriptional promoter operably linked to RRN3 polynucleotide, which hybridizes to a DNA encoding a Rrn3 polypeptide and DNA encoding a functional fragment thereof. The claims are further limited to DNA encoding a Rrn protein or a fragment thereof that stimulates ribosomal RNA transcription. The dependent claims are further drawn to other nucleic acid molecules and vectors comprising the above sequences and host cells transfected with them.

The specification discloses isolated cDNA sequences, SEQ ID NO:1, which encodes a polypeptide sequence, SEQ ID NO:2. The claims, as written, however, encompass polynucleotides which vary substantially in length and also in nucleotide composition. The broadly claimed genus additionally, encompasses human RRN3 gene, as well as other human genes such as alternatively splice gene products, RRN3 genes from chimpanzee, and other higher eukaryotic species other than human, or polymorphic RRN3 gene. The instant disclosure of a single species of nucleic acid, SEQ ID NO:1 does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

It is concluded that applicant adequately describes DNA molecules of SEQ ID:1.

35 U.S.C. 112, First Paragraph, Scope Rejection

Claims 1,2, 4, and 7-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while ***being enabling for how to make*** the DNA of SEQ ID:1 for encoding full-length human Rrn protein with potential to stimulate ribosomal RNA transcription, does not reasonably provide enablement for how to use SEQ ID NO:1 (see Utility rejection below) or how to make and use any other DNA molecules that hybridizes to SEQ ID NO:1 or fragment of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to isolated nucleic acid which hybridizes under the specified conditions in the claims to SEQ ID NO:1 or to DNA encoding SEQ ID NO:2 (claims 1-5) and to expression construct with a transcriptional promoter and stop condon operably linked to RRN3 polynucleotides which hybridizes under the specified conditions (claim 7) to a isolated DNA encoding a Rrn3 polypeptide.

The specification teaches that the DNA sequence of SEQ ID:1 can be used to produce SEQ ID NO:2 protein that ***might*** (the specification does not describe the protein indeed stimulate rRNA transcription but only speculates the activity) stimulate transcription of ribosomal RNA. The specification does not teach any other uses of DNA that does not encode a protein that is involved in ribosomal RNA transcription. The nucleic acids claimed in claim 1,2, 4, 7-24 are not enabled because the specification does not provide guidance how to use plethora of nucleic acid molecules

that hybridizes to SEQ ID NO:1 or to DNA encoding a functional Rrn3 polypeptide fragment thereof. Are these unknown DNA molecules retain structural similarity to SEQ ID:1 and encode a protein that retains the function "stimulates ribosomal RNA transcription"? One cannot extrapolate the teaching of the specification to the claims because it is well known in the art that even slight modifications in a peptide or protein structure can have significant and unpredictable effects on biological activity. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out biological activity and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid (including conservative substitutions) in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or even with conservative glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. The specification does not teach the specific structures responsible for stimulation of ribosomal transcription, nor

provide guidance as to what changes in the structure can be made retaining the stimulation of ribosomal transcription activity. Considering the broad scope of the claims, the limited teachings of the specification regarding which could be changes in the structures of the DNA to retain the potential to stimulate rRNA transcription, and lack of working examples, it is concluded that undue experimentation would be required to enable the full scope of the claims.

Claim Rejections - 35 USC § 101

Claims 1-5, and 7-24 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Claims 1-5, and 7-24 are directed to an isolated polynucleotide encoding a novel human protein, vector comprising the polynucleotides, host cells comprising the vector, and method of recombinantly producing the encoded polypeptide. The specification discloses how to make SEQ ID NO:1 encoding SEQ ID NO:2 protein that complement the rrn3 null mutation in yeast (page 65, lines 18-21). This disclosure is not sufficient to determine what the biological function(s) of human Rrn3 gene product is. The rescuing of the lethal yeast rrn3 null mutation by human Rrn3 does not tell how the human Rrn3 works in human body. The specification at page 2 lines 11-27 summaries the recent publications regarding yeast Rrn3 protein and the specification at page 2 lines 24 and 25 says that "the specific function of Rrn3 polypeptide is as yet unknown." Moorefield et al (25 April 2000, Proc. Natl. Acad. Sci. USA, Vol. 97, pages 4724-4729) teach that the function of hRrn3 is unknown. See page 4728, left column, line 14 from the bottom of the page. Further, Milkereit et al (IDS, 1998, The EMBO Journal, Vol. 17, pages 3692-3703) at pages 3692 and 3693 teach that multiple transcription factors stimulate rRNA transcription, therefore human Rrn3's ability to stimulate rRNA transcription is not specific to Rrn3 protein.

Further, sequence similarity to yeast Rrn3 protein does not necessarily mean that human Rrn 3 protein has same biological function to yeast Rrn3 because Scott et al (Nature Genetics, 1999, 21:440-443) teach that the function of newly identified gene

products is unpredictable even when the database searches reveal significant homology to proteins of known function. Scott et al teaches that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. states that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must

be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of the newly identified instantly claimed protein and for the DNA molecule encoding the protein.

The specification contains assertions that the claimed invention, human Rrn3 polypeptide encoded by claimed invention, the antibody to Rrn3 polypeptide, agonists and antagonists of the protein can be used for treatment and prevention of disease involving cell hyperproliferation and hypoproliferation (pages 46 and 47). Other disclosed utilities are gene therapy (pages 37-42), antisense therapy (page 42), and diagnosis and screening of diseases (pages 51-54), screening for agonists and antagonists (page 54). These utilities are not specific to the claimed invention. The specification does not support a credible, specific and substantial utility because the specification does not teach a relationship to any specific disease or establish any involvement of the claimed invention in the etiology of any specific disease or does not teach what the function(s) of the protein encoded by the claimed invention. The specification asserts that the claimed polypeptides are involved in cell proliferation but Schnapp et al (IDS, 1990, The EMBO Journal, Vol. 9 pages 2857-2863) teach at the Introduction that "regulation of cell proliferation is a complex process" involving a lot of proteins. The specification does not disclose a correlation between any specific proliferative disorder and an altered level or form of the claimed polynucleotides or polypeptide encoded by the claimed invention. Also, the specification does not show

whether the claimed polynucleotides or polypeptides encoded by the claimed invention is overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control. Therefore, the disclosed utilities are not considered specific, credible, and substantial because they are just invitations for one skilled in the art to figure out how the protein functions or what the biological activities are for the claimed invention. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not how to find out how to use it for themselves. The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

35 U.S.C. § 112, First Paragraph

Claims 1-5, and 7-24 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know ***how to use*** the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Misook Yu whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu, Ph.D.
August 8, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600